REMARKS

Applicant has amended claim 1 such that it refers to "a method of producing a graft of non-hematopoietic tissue in damaged or diseased tissue of a subject in need thereof, which comprises isolating stem cells from a peripheral blood sample of donor by apheresis…." Applicant has also amended claim 14 to recite, "a method of treating damaged or diseased striated muscle tissue of a subject by producing a graft of non-hematopoietic tissue in the damaged or diseased striated muscle tissue…", and applicant has amended claim 31 to recite, "a method for treating in an ischemic organ in a subject by producing a graft of non-hematopoietic tissue in said ischemic organ…." Support for these amendments is found on e.g., page 3, lines 20-21 wherein applicant discloses:

> the implanted stem cells proliferate and differentiate to form stable grafts at the site of damage or disease;

page 4 line 26 to page 5, line 2 which states:

> In another aspect, the invention is directed to a method of treating striated muscle tissue that has suffered damage or disease. Again, apheresis is used to isolate stem cells from the peripheral blood. The isolated cells are then implanted at the desired site of damage or disease. The implanted peripheral blood stem cells proliferate and differentiate into striated muscle cells, and form stable grafts at the site of damage or disease.

and on page 8, lines 16-24 wherein applicant states:

> Repopulation and/or augmentation of the affected area is accomplished by introducing stem cells to the site of damage or disease. It has been shown that stem cells obtained from peripheral blood can reconstitute the hematopoietic tissue of subjects undergoing cytoreductive therapy such as chemotherapy or radiation therapy [citations omitted.] In the present methods, autologous transplantation of stem cells isolated from peripheral blood is used to repopulate or augment non-hematopoietic tissues or organs. (emphasis added)

Claims 1, 5, 6, 10-14, 17, 18, 20, 22, 23, 27-31, 35, 37, 38, 42-44 and 45 stand rejected under 35 U.S.C. 102(b) for purportedly being anticipated by Kocher et al., "Neovascularization of ischemic myocardum by human bone marrow derived angioblasts prevents cardiomyocyte

apoptosis, reduces remodeling and improves cardiac function", *Nature Medicine* (April 2001) Vol. 7, No. 4, pp 430-436 ("Kocher"). In view of the amendments to the claims and the following remarks, applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Kocher is directed to neovascularization in tissue, thus reconstitution of hematopoietic tissue, and not to methods for the production of a graft of non-hematopoietic tissue as set forth in applicant's claims. Kocher isolates a population of stem cells that are enriched for endothelial precursors having the properties of hemangioblasts (page 430, right col.) for induction of vasculogenesis and angiogenesis. In particular, Kocher fractionates the peripheral blood sample and isolates stem cells expressing the hematopoietic lineage marker CD34. As such, non-hematopoietic stem cells, e.g., mesenchymal stem cells, which are multipotent cells that can be induced under appropriate conditions to differentiate into diverse tissues such as bone, cartilage, fat, tendon and muscle that do not express hematopoietic lineage markers, such as CD34 or CD45 (see Kocher page 430, left col.), are depleted in Kocher's stem cell sample. Thus, Kocher only demonstrates that a peripheral blood sample enriched *in vitro* for endothelial precursors are useful for reconstituting hematopoietic tissues. Kocher does not teach or suggest that any peripheral blood stem cells are useful for reconstituting non-hematopoietic tissues. In contrast, applicant teaches the use of peripheral blood stem cells for producing a graft of non-hematopoietic tissue in a damaged or diseased tissue.

In view of the amendments to the claims and the forgoing remarks, applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. 102(b) for purportedly being anticipated by Kocher et al.

Claims 1, 9-14, 17, 18, 21, 26-31 and 41-45 stand rejected under 35 U.S.C. 102(b) for purportedly being anticipated by Kalka et al., "Transplantation of *ex vivo* expanded endothelial progenitor cells for therapeutic neovascularization," *PNAS* (March 28, 2000) Vol. 97, No. 7 pp 3422-3427. Kalka, like Kocher, is directed to neovascularization and thus reconstitution of hematopoietic tissue, rather than producing a graft of non-hematopoietic tissue. Kalka expands human peripheral blood mononuclear cells (PBMCs) in culture under conditions that produce a population of differentiating cells of the endothelial lineage, transplants the endothelial cell

precursors into mice with hindlimb ischemia and assays for blood flow recovery and capillary density (p. 3424, right col.). Applicant's methods relate to the production of grafts of non-hematopoietic tissue by implanting stem cells, and to the treatment of damaged or diseased striated muscle or an ischemic organ by producing a graft of non-hematopoietic tissue, none of which are taught by Kalka.

In view of the amendments to the claims and the foregoing remarks, applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 102(b) in view of Kalka.

Claims 1-45 stand rejected under 35 U.S.C. 103(a) for purportedly being unpatentable over the combination of Kocher, Kalka and Lagasse et al., "Purified hematopoietic stem cells can differentiate into hepatocytes in vivo," *Nature Medicine* (November 2000) Vol. 6, No. 1, pp. 1229-1234("Lagasse"). Applicants respectfully disagree.

As discussed *supra*, both Kocher and Kalka disclose methods for neovascularization and thus relate to reconstitution of hematopoietic tissue. Neither document teaches or suggests producing grafts of non-hematopoietic tissue by using peripheral blood stem cells. Lagasse does not compensate for the deficiencies of Kolcher and Kalka. The Examine states "... the reference by Lagasse et al. teaches that blood or hematopoietic stem cells can differentiate into hepatocytes (title)" (Office Action page 7). However, the title only states:

> "Purified hematopoietic stem cells can differentiate into hepatocytes in vivo"

The title does not state that blood can differentiate into hepatocytes nor does it recite the source of the hematopoietic stem cells that purportedly gave rise to hepatocytes. In fact, the source of Lagasse's hematopoietic stem cell source is identified on page 1230, left col., which states that that the cells are highly purified hematopoietic stem cells (HSCs) isolated from the bone marrow, and not isolated from peripheral circulating blood. Lagasse states:

> HSCs have been rigorously and directly identified; in the BA mouse strain, HSCs represent a rare population of 0.01-0.05% of whole bone marrow that can be reproducibly isolated using a combination of 13 distinct cell surface markers [citations omitted].

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> We isolated HSCs from the bone marrow of normal adult [male mice] by fluorescence-activated cell sorting (FACs)(Fig. 2). (emphasis added)
>
> Lagasse, page 1230, left col. paragraphs 1 and 2

Lagasse does not teach one of skill in the art to isolate stem cells from peripheral blood nor does Lagasse teach using peripheral blood stem cells for producing grafts of non-hematopoietic tissue. Furthermore, based on Lagasse's teachings one of skill in the art would have no reason to expect that stem cells found in the circulating peripheral blood would be useful for producing grafts of non-hematopoietic tissue: especially in view of the results from Kolcher and Kalka, who only disclose that endothelial stem cells isolated from peripheral blood produce neovascularization. Thus, Lagasse, in combination with Kocher and Kalka fail to teach or suggest applicant's invention as claimed.

In view of the amendments to the claims and the foregoing remarks applicant respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. §103(a) in view of Lagasse, Kocher and Kalka.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

If additional fees are due, please charge our Deposit Account No. 50-0624, under Order No. WO-BSX 233/10408840 from which the undersigned is authorized to draw.

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Respectfully submitted,

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